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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
ZEMAN, ROBERT A

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 07/07/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/393,302	HOVANESSIAN ET AL.	
	Examiner	Art Unit	
	Robert A. Zeman	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-39* is/are pending in the application.

4a) Of the above claim(s) *1,7,8,11,12 and 14-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4-6,9,10,13 and 24-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) *1,2 and 4-39* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4-25-2003 requesting the entry of the amendment filed on 3-21-2003 has been entered. Hence, claims 2, 4-6, 9-10, 13 and 24 have been amended. Claims 25-39 have been added. Claims 1-39 are pending. Claims 1, 7-8, 11-12 and 14-23 remain withdrawn from consideration. Claims 2, 4-6, 9-10, 13, 24 and 25-39 are currently under examination.

Objections Withdrawn

The objection to claims 6, 9, 13 and 24 as being in improper multiple dependent form is withdrawn in light of the amendment thereto.

Objections Maintained

The objection to claim 10 as being in improper multiple dependent form is maintained for reasons of record. As outlined previously, a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n).

The objection to the drawings outlined on the PTO-948 form attached to the previous Office action (Paper No. 24) is maintained. Applicant states in his response that corrected

drawing were attached to said response (Paper No. 24.5). To date, no corrected drawings have been received.

Claim Rejections Withdrawn

The new matter rejection of claims 2, 4-6, 9-10, 13 and 24 under 35 U.S.C. 112, first paragraph, is withdrawn in light of the amendment thereto.

The rejection of claim 2 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the term "alters and/or prevents" is withdrawn in light of the amendment thereto.

The rejection of claim 2 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the term "peptidic fragment" alters and/or prevents" is withdrawn in light of the amendment thereto.

The rejection of claim 2 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the term "homologous" is withdrawn. Applicant's assertion that said term refers to polypeptides containing one or several amino acid additions, deletions or substitutions in the sequence of P95/nucleolin wherein substitution mutations must be made with equivalent amino acids (i.e. substitutions cannot decrease the ability of said peptide to bind either 5[Kψ(CH_2N)PR]-TASP, the V3 loop peptide, gp120 of HIV-1 or gp125 of HIV-2.

The rejection of claim 4 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the phrase "pseudopeptide which is homologous" is withdrawn in light of the amendment thereto.

Claim Rejections Maintained and New Grounds of Rejection

35 USC § 112, Written Description Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claims 2, 4-6, 9-10, 13, 24 and 24-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 2 and 38 recite the limitation "a fragment of cell surface P95/nucleolin". Moreover, claim 4 is drawn to inhibitor molecules that are homologues of the fragments of claim 2.Therefore, the aforementioned claims are directed to encompass, any fragment of P95/nucleolin, corresponding sequences from other species, mutated sequences, allelic variants, splice variants, sequences that have a recited degree of identity (similarity or homology), and so forth. None of these sequences meet the written description provision of 35 USC 112, first paragraph. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now*

claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

Written description of an invention requires "a precise definition, such as by structure, formula, chemical name, or physical properties." *Eli Lilly*, 119 F.3d at 1566, 43 USPQ2d at 1404. The specification does not set forth any of these definitions for other polypeptides (i.e. fragments) which fall within the scope of the claims. An applicant may also show written description of an invention by combining structure, physical properties, or chemical characteristics with a known or disclosed specific function. However, no specific function or activity has been ascribed to any one of the claimed fragments in the specification, as filed.

Therefore, only the full -length P95/nucleolin protein, not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variable. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 4-6, 9-10, 13, 24 and 25-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This is a new grounds of rejection necessitated by amendment.

Claims 2 and 38 are rendered vague and indefinite by the use of the phrase "alters the interaction". It is unclear what is meant by said phrase. What constitutes an alteration? Moreover, is the "interaction" Applicant referring to specific binding or some other process?

Claim 4 is rendered vague and indefinite by the use of the term "homologous to the inhibitor molecule of claim 2". It is unclear what is meant by said term. Claim 2 is drawn (in part) to homologues of P95/nucleolin fragments. Therefore, the rejected claim is drawn to a homologue of a homologue. It is unclear what polypeptides would meet the requirements of said limitations.

Claims 2 and 38 are rendered vague and indefinite by reciting improper Markush language. Said claims are drawn to a single inhibitor molecule but the Markush group recites the possibility of multiple molecules as evidenced by the phrase "chosen from at least one of". Moreover, the last member of the Markush group listed in claim 38 should be preceded by the article "or".

Claim 39 is rendered vague and indefinite by the use of the term "produced by chemical synthesis or recombinant techniques. It is unclear whether said phrase is referring to the pseudopeptide or the fragment of cell surface P95/nucleolin.

35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The instant invention is drawn to various fragments of nucleolin that function to inhibit the interaction between gp120 of the HIV retroviruses and the V3 loop.

Claims 2, 4, 6, 9-10, 13 and 24-39 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Callebaut et al. (Virology Vol. 218, No. 1, pages 181-192, 1996) for the reasons outlined in the previous Office action in the rejection of claims .2-4, 6, 9-10, 13 and 24.

Applicant argues:

1. Callebaut et al. only discusses the TASP pseudopeptide.

2. Callebaut et al. do not teach or suggest the use of peptidic fragments of extracellular or cytoplasmic (now cell surface) nucleolin or pseudopeptide homologous to them.

3. Applicant does not claim the TASP pseudopeptide taught by Callebaut.

4. The specification defines a homologous polypeptide as having one or more amino acid additions, deletions and/or substitutions. Hence an unrelated protein cannot qualify as homologous under said definition.

5. The TASP pseudopeptide is structurally unrelated to P95/nucleolin and thus cannot qualify s homologous.

Applicant's arguments have been fully considered and deemed non-persuasive.

The limitations of the rejected claims require that a given peptide be a fragment of P95/nucleolin or be a homologue of said fragments. Said peptide must also "alter the interaction between a cellular receptor and gp120 of the HIV-1 virus". As written, the claimed fragment can be as small as a single amino acid since no functional language is recited as long as it "alters" the interaction between a cellular receptor and gp120. The TASP pseudopeptides are is encompassed by the instant invention since it is a peptide that is a minimal fragment of P95/nucleolin that inhibits the interaction of a cellular receptor and gp120 (see pages 184-188). It should be noted that the claims recite no language limiting the means by which said interaction is altered.

35 USC § 102

Claims 2, 4, 6 and 38-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Srivastava et al. (FEBS Letters, Vol. 250, No. 1, pages 99-105, 1989).

The instant claims are drawn to fragments of cell surface P95/nucleolin and homologues of said fragments.

Srivastava et al. disclose the cDNA of human nucleolin. Since the bovine probes used were derived from the total RNA of the adrenal medulla, all forms of nucleolin would be utilized (see materials and methods section). As outlined previously, Srivastava et al. disclose the complete nucleotide and amino acid sequence for human nucleolin (see page 101). Srivastava et al. further disclose a comparison between nucleolin from humans, chickens and hamsters. Since the entire nucleolin protein was incorporated in the cDNA library (see page 109), in absence of evidence to the contrary, said library would generate all of the peptides/fragments of the claimed invention.

35 USC § 103

Claims 5, 9-10, 13 and 24-37 are rejected under 35 U.S.C. 103(a) as obvious over Srivastava et al. (FEBS Letters, Vol. 250, No. 1, pages 99-105, 1989) for the reasons outlined in the previous Office action in the rejection of claims 2, 4-6, 9-10, 13 and 24.

Applicant argues:

1. The amended claims read on extracellular or cytoplasmic nucleolin, not the nuclear nucleolin described in the cited reference.

2. The amended claims are drawn to cell surface nucleolin and hence cannot be rendered obvious by said reference.

3. Applicant has demonstrated post filing that cell surface nucleolin is distinguishable from nuclear nucleolin.

Applicant's arguments have been fully considered and deemed non-persuasive. Srivastava et al. disclose the cDNA of human nucleolin. Since the bovine probes used were derived from the total RNA of the adrenal medulla, all forms of nucleolin would be utilized (see materials and methods section). As outlined previously, Srivastava et al. disclose the complete nucleotide and amino acid sequence for human nucleolin (see page 101). Srivastava et al. further disclose a comparison between nucleolin from humans, chickens and hamsters. Since the entire nucleolin protein was incorporated in the cDNA library (see page 109), in absence of evidence to the contrary, said library would generate all of the peptides/fragments of the claimed invention. While Srivastava et al. do not specifically describe the using said peptides/fragments for the inhibition of ph120/nucleolin binding, it would be an inherent property of said fragments. Determination of biological/chemical properties of each peptide/fragment would have been obvious to one of ordinary skill in the art since it constitutes a standard laboratory practice. Additionally, since Srivastava et al. knew the sequences of the cDNA fragments (see page 109), it would have been obvious to one of ordinary skill in the art to modify said sequences in order to enhance the stability etc of said peptide. One would have been motivated to make such modifications in order to protect said peptides from endogenous protease thus increasing the half-life of said peptides.

With regard to Applicant's arguments that cell surface nucleolin is distinguishable from nuclear nucleolin, it should be noted that the reference upon with Applicant has based his argument is not of record. However, even if one is able to distinguish between the full-length proteins, the instant claims are drawn to fragments of cell surface P95/nucleolin. One of ordinary skill in the art would assume, in the absence of evidence to the contrary, that there would be an extremely high degree of sequence homology between the two forms of nucleolin and hence many "fragments" would be identical.

Claims 2, 4-6, 9-10, 13 and 24-39 are rejected under 35 U.S.C. 103(a) as obvious over Rankin et al. (Nucleic Acids Research, Vol. 21 No. 1, page 169) for the reasons outlined in the previous Office action in the rejection of claims 2, 4-6, 9-10, 13 and 24.

Applicant argues:

1. Rankin et al. teaches that nucleolin is a nucleolar specific protein that assists in the process of pre-ribosomal RNA as the ribosomes are assembled.

2. The amended claims read on extracellular or cytoplasmic nucleolin, not the nuclear nucleolin described in the cited reference.

Applicant's arguments have been fully considered and deemed non-persuasive.

With regard to Point 1, Rankin does not, contrary to Applicant's assertion, teach that nucleolin is a nucleolar specific protein that assists in the process of pre-ribosomal RNA as the ribosomes are assembled. Rankin et al. merely speculate on a possible function of nucleolin. Regardless of said statement, the cDNA used to determine the nucleolin sequences was derived from ovary cells and hence would contain all forms of nucleolin.

With regard to Point 2, Rankin et al. do not disclose the source of the nucleolin used to determine the cDNA sequence as being nuclear. In fact, Rankin et al. disclose that the cDNA sequence was constructed from "overlapping sequences recovered from an ovary cDNA library". This would indicate that the library was constructed using total RNA was used instead of only nuclear RNA.

As outlined in the previous Office action, Rankin et al. disclose the fully-length cDNA sequence of nucleolin. Rankin et al. differ from the instant invention in that they do not disclose specific peptides. However, it would have been obvious to one of ordinary skill in the art to use the disclosed cDNA sequence to produce polypeptides since it is standard laboratory practice to determine the functions of various sequences etc and to incorporate the resulting peptides in compositions. Additionally, the cited reference reads on all the rejected claims since said claims recite open claim language.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (703) 308-7991. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (703) 308-3909. The fax phone numbers for the

organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Robert A. Zeman
July 2, 2003